Review article

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THE EMERGING BENEFITS OF RENALASE BASED ON PRECLINICAL STUDIES: THE CURRENT PERSPECTIVE

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The Mammalian Gene Collection Project enabled the discovery of a novel kidney enzyme, subsequently named renalase in 2005. Renalase was initially identified in proximal renal tubules, however the following research reveals its broad pattern of tissue expression. Evidence demonstrates its cytoprotective properties, establishing it as a survival element in various organ injuries (heart, kidney, liver, intestines), and as a significant anti-fibrotic factor, owing to its, in vitro and in vivo demonstrated pleiotropy to alleviate inflammation, oxidative stress, apoptosis, necrosis, and fibrotic responses. Effective anti-fibrotic therapy may seek to exploit renalase's compound effects such as: lessening of the inflammatory cell infiltrate (neutrophils and macrophages), and macrophage polarization (M1 to M2), a decrease in the proinflammatory cytokines/chemokines/reactive species/growth factor release (TNF-α, IL-6, MCP-1, MIP-2, ROS, TGF-β1), an increase in anti-apoptotic factors (Bcl2), and prevention of caspase activation, inflammasome silencing, sirtuins activation, and mitochondrial protection, suppression of epithelial to mesenchymal transition, a decrease in the pro-fibrotic markers expression (α-SMA, collagen I, and III, TIMP-1, and fibronectin), and interference with MAPKs signaling network, most likely as a coordinator of pro-fibrotic signals. Mounting studies set the stage for renalase's pleiotropy to the level of cancer, particularly as a molecular driver for specific cancers, such as pancreatic, melanoma, renal, and breast cancer. The observation of renalase's enzymatic activities, particularly its interference with catecholamines metabolism, and regulation of plasmatic concentration, initially lead to the conclusion that renalase may significantly affect blood pressure regulation.

This review provides the scientific rationale for renalase's scrutiny regarding various organ injuries, and there is great anticipation that these newly identified pathways are set to progress one-step further. Although substantial progress has been made, indicating renalase's therapeutic promise, more profound experimental work is required to resolve the accurate underlying mechanisms of renalase before any potential translation to clinical investigation.

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Introduction

The Mammalian Gene Collection Project enabled the discovery of a novel kidney enzyme, subsequently named renalase (1, 2) in 2005. Renalase was initially identified in proximal renal tubules (3-5), however the following research reveals its broad pattern of tissue expression, which includes the heart (6-13), brain (14, 15), liver (16, 17), pancreas (18), intestines (19), skeletal muscles (20) and the eyes (21). Mounting studies that followed set the stage for renalase's pleiotropy to the level of cancer, particularly as a molecular driver for specific cancers, such as pancreatic (22, 23), melanoma (24, 25), renal (26) and breast cancer (27). However, the most intriguing of the emerging findings indicated some promising benefits regarding renalase's expression in the human placenta, from the earliest stages of its development, suggesting its relevant role in human growth and gestation (28). The observation of renalase's enzymatic activities, particularly its interference with catecholamines metabolism, and regulation of plasmatic concentration, initially lead to the conclusion that renalase may sig-

nificantly affect blood pressure regulation (29). Given its more recent behavior as a pro-survival agent, particularly in the event of various organ injuries, and its potential to lessen the extent of an acute injury, renalase was assessed as a potentially relevant therapy option for diverse pathologies (30-44).

This review comprehensively summarizes the most up-to-date of results of preclinical studies, indicating the discovery that renalase functions as a pleiotropic molecule that likely protects different organs (kidney, heart, liver, intestines) against ischemic and toxic injuries. It also provides insight into renalase's role as a survival factor for tumor cells, since we now know that dysregulation of renalase signaling enables the survival and growth of melanoma and pancreatic cancer cells.

Renalase's biology

Renalase, named for its discovery, has been initially identified as a flavin adenine dinucleotide (FAD)-dependent amine oxidase, synthesized and secreted by the kidneys (1, 2, 29), resulting in a plasmatic concentration of approximately 5 μg/mL. This flavoprotein has been determined to function as a monoamine oxidase (MAO)-C, showing that less than 14% of amino acids identity with MAO-A. However, up until now, renalase has been identified as only a monoaminoxidase found in the blood, that, when *in vitro*, degrades catecholamines (29). Abundant research evidences the lack of renalase in patients suffering from chronic kidney disease. This perception poses the hypothesis that renalase deficiency accounts for the significant catecholamine excess which has often been observed in chronic kidney disease, as well as subsequent cardiovascular complications. Moreover, by metabolizing catecholamines, renalase likely decreases blood pressure, cardiac contractility, and heart rate, and prevents the compensatory increase in peripheral vascular tone (2, 29). It is however acknowledged that renalase activity in the blood reflects the level of the sympathetic tone, while in the setting of brief peaks of catecholamine blood levels, the activity, secretion, and synthesis of renalase are up-regulated resulting in significant hemodynamic effects, particularly *in vivo* (29). It is entirely possible that catecholamines induce a conformational change in the prorenalase molecule, or it may indicate proteolytic cleavage of prorenalase results in the rapid activation of renalase (29). It is widely accepted that plasma catecholamines and sympathetic tone are permanently increased in patients with chronic kidney disease, even after successful renal transplantation. This phenomenon likely contributes to the pathophysiology of hypertension, left ventricular hypertrophy, and ultimately, cardiac failure. The results of the aforementioned research give rise to hope that renalase replacement therapy may be highly beneficial in patients who are suffering with kidney disease. Additional research recognizes renalase's health benefits, extending far beyond the kidneys (heart, liver, intestines, skeletal muscles) as aforementioned, whereas its wide range of relevance has posed important questions as to whether renalase provides any additional advantages, far beyond only the catalytic molecule.

An outstanding advancement in renalase's pathophysiology was made upon the discovery that this protein exerts potent cyto protection, independent of amine oxidase activity. Indeed, both *in vitro* and *in vivo*, it has been documented that renalase effectively protects against toxic injury, such as cisplatin- and hydrogen peroxide-induced necrosis, by activating the intracellular signaling network, functioning entirely separately from its catecholamines-metabolizing properties (4). The up-regulation of protein kinase B (PI3K/Akt), mitogen-activated kinases (MAPKs), and extracellular signal-regulated kinase 1 and 2 (ERK ½), as well as the down-regulation of c-Jun N-terminal kinases is evidenced to be critical. These findings promote renalase protection in the animal model of acute kidney injury (AKI) (4). This observation supports subsequent cross-linking research in resolving a potential receptor for extracellular renalase. Accordingly, the plasmatic membrane calcium ATPase 4b (PMCA4b) has been identified as the receptor for renalase that, following its activation, sets in motion a choir of various signals from within the cells, presumably in order to promote its protective properties. In line with these findings, additional results indicate that renalase, by targeting its receptor, activates numerous downstream signaling, including acting as a signal transmitter as well as the activator of transcription (STAT3), NOS, NF-κβ, c-AMP, Ca^{2+}, p38, and Ras/Raf/MEK/ERK (37, 45). In line with the aforementioned, there are some transcriptional factors established as regulators of renalase gene expression, including TNF-α, HIF-1α, NF-κβ, STAT3, Sp1, some of which are ironically related to inflammatory responses (43, 45, 46-50). Among these regulatory pathways of particular clinical relevance may be renalase's positive feedback loop with STAT3 (45), a recognition that may be further investigated in the field of cancer pathology. Accordingly, renalase's link with HIF-1α, in which renalase mediates the protective effects of HIF-1α, may be valuable in the settings of ischemia/reperfusion injuries (at least in the heart and the kidneys).

The newly discovered recognition that factors included in cell proliferation, apoptosis, inflammation and overall protection are very closely linked to renalase's pathophysiology presumably implies diverse and distinct renalase cell signalization pathways, providing this molecule a multifaceted function in tissue homeostasis and various organ protection.

Renalase and the kidney

A growing body of evidence for the pro-survival effects of renalase in the field of acute kidney injury nominates this protein for more comprehensive scrutiny regarding the resolution of acute injuries (51, 52). For instance, contrast-induced nephropathy, and the possible occurrence of chronic

kidney disease represents an ongoing concern in the field of invasive cardiology. Acknowledging that renalase performs a pivotal role in blood pressure regulation and cellular survival, renalase has been assigned the competence of being a potential biomarker for AKI, indicating the existing loss of renal function and specifying disease severity (52). Namely, lack of the renalase gene (44) in animals exposed to renal ischemia reperfusion injury leads to significant renal tubular necrosis, inflammation and apoptosis, while, in ischemic and toxic (cisplatin-induced) AKI recombinant renalase supplementation, these changes are alleviated (44). In accordance, renalase-knocked-out mice subjected to cisplatin develop an increase in their plasmatic creatinine levels, significantly improve their renal injury score, the degree of apoptosis, and infiltration of macrophages. *In vitro* (HK-2 cells) recombinant renalase administration protects the cells against cisplatin- and oxidative (hydrogen peroxide-induced damage) injury, and furthermore, delays ischemic damage (4). Pivotal conclusions of the aforementioned study are that renalase prevents AKI, independent of its amine oxidase activity, and that its intracellular signaling is enabled via the rapid increase in phosphorylation of extracellular signal-regulated kinase 1 and 2 (ERK), and p38 MAPK signaling. At the same time, it decreases the phosphorylation of C-Jun N-terminal kinases. Subsequently, it has been demonstrated that renalase exerts its protective effects through ERK1/2, p38, and PI3K/Akt signaling networks by activating its receptor which has been previously identified as PMCA4b (35, 37, 40), (see above). More recent evidence of renalase's effects in cisplatin-induced AKI provides another important feature of its protective mechanism (5). However, both *in vitro* and *in vivo* it has been established that renalase significantly interferes with mitochondrial dynamics, as well as sirtuin 3 (SIRT3) levels by suppressing mitochondrial fission and reactive oxygen species production (5). It is worth noting that sirtuin 3 represents one of the mitochondrial deacetylases, presumably protecting all aspects of mitochondrial metabolism and the homeostasis of multiple organs (53). Its dysfunction is accordingly associated with age-related diseases, such as cancer, heart disease and metabolic diseases, suggesting sirtuin 3 as an applicable therapeutic target. It may be hypothesized that renalase, by functioning in a sirtuin 3-dependent manner, may establish various organ protection, far beyond protecting only against cisplatin-induced AKI.

The protective effects of renalase in the animal model of renal ischemic/reperfusion injury underscores its role as a protector of the kidneys. Ischemic preconditioning, prior to ischemic kidney injury, lessens renal inflammatory response, thus alleviating the degree of tubular necrosis and oxidative stress, at least in part, by renalase up-regulation (54). These remarks provide the hypothesis that renal ischemic preconditioning protection is mediated by renalase, and that renalase up-regulation is achieved by activation of TNF-α/NF-$\kappa\beta$ signaling. Positive effects of this process such as amelioration of the renal function, attenuation of tubular injury, and reduction of ROS and inflammation were abolished by simply silencing the renalase gene (54). This research emphasizes the renoprotection effects of renalase administration against contrast-induced nephropathy, providing the hypothesis that renalase therapy may represent clinically administered, contrast-induced nephropathy prevention. Subsequent research serves to additionally confirm that renalase pre-treatment markedly preserves renal function, mitigates tubular necrosis, oxidative stress, apoptosis, and inflammation in animals exposed to contrast-induced nephropathy (3), providing another indicative support for renalase's anti-oxidative, anti-necrotic, and anti-inflammatory properties. In line with these findings, renalase exerts have confirmed *in vitro* protection against loversol-induced cytotoxicity, which significantly abolishes caspase-3 activity, reactivating oxygen species generation and H_2O_2-induced apoptosis, hinting at the pivotal mechanisms of renalase's cytoprotection, by suppressing oxidation, apoptosis and inflammation mechanisms (43).

As a result, renalase anti-fibrotic properties have been further established and confirmed, and two meaningful pathways are proposed (30, 31). It is suggested that renalase alleviates renal fibrosis by reducing the production of reactive oxygen species, and perhaps even more importantly by suppressing oxidative-stress-induced epithelial-mesenchymal transition (EMT). It has to be mentioned that the epithelial-mesenchymal transition (EMT) represents an evolutionary process whereby epithelial cells acquire mesenchymal fibroblast-like features, such as decreased intercellular adhesion and enhanced mobility, making it one of the essential wound healing processes (55). The sequence of actions such as wound healing, tissue regeneration, and organ fibrosis represents a reparative-associated process in response to chronic inflammation-induced fibroproliferation that eventually leads to organ fibrosis and failure. Accordingly, beyond MDA suppression and the restoration of SOD expression, the administration of renalase abolishes oxidative stress-induced α-SMA, fibronectin, and collagens (I and III), thus restoring E-cadherin expression (as a marker of epithelial cells), in a dose-dependent fashion (30), as well as restoring H_2O_2-mediated epithelial-mesenchymal transition and fibrosis *in vitro*. The other study, however, confirms the same anti-fibrotic effects of renalase, but provides another plausible mechanism of its protection, namely by inhibiting activation of ERK 1/2 signalization (31). This study, however, explores how renalase therapeutic effects in animals subjected to unilateral ureteral obstruction, and assesses the capacity of renalase to suppress the transforming growth factor-β1 (TGF-β1)-induced EMT in the culture of proximal renal tubular epithelial cells (HK-2). Renalase significantly mitigates the progression of interstitial fibrosis in kidneys, via EMT inhibition, whereas renalase's primary activity is reveled to be the inhibition of the ERK 1/2 pathway. This data, collectively, provides additional theoretical support that the administration of rena-

lase in chronic kidney disease patients may effectively serve to mitigate the disease's progression.

Renalase and the heart

The initially identified effects of renalase in kidney pathology were additionally confirmed in preclinical models of acute myocardial ischemia (42). The study revealed that the administration of recombinant renalase significantly reduced the size of the necrotic field, and that cardiac hypertrophy is lessened, due to renalase application. (42). Subsequent research demonstrates that renalase represents a target gene of hypoxia-inducible factor-1α (HIF-1α) (43). The same study however, identifies that renalase down-expression in the heart results in a greater significance of ischemic/reperfusion injury, increased size of necrosis and aids in the prevention of decreased ejection fraction (EF). The studies that follow, beyond confirming the pro-survival properties of renalase, suggest the mechanisms of its cyto-protection, which are most likely administered by reducing inflammation, apoptosis, and necrosis, and by suppressing fibrotic responses. It is initially confirmed that renalase protects the cardiomyocytes against ischemia and reperfusion injury by lessening the level of necrosis and apoptosis, (6), supposing renalase as a novel cardiovascular drug for ischemia/reperfusion injury. In the preclinical model of chronic kidney disease (rats were subjected to 5/6 nephrectomy), renalase administration significantly preserves cardiac phenotype, including left ventricular (LV) hypertrophy prevention, LV hydroxyproline concentration (as a measure of cardiac fibrosis) and LV papillary muscle dysfunction (7). Such promising results opens up the possibility for renalase utilization in cardio-renal pathology, particularly in patients with chronic kidney diseases who have developed cardiac hypertrophy. Similar study models (41) reveal that renalase attenuates the progression of cardio-renal syndrome, whereas the administration of recombinant renalase reduces proteinuria, glomerular hypertrophy, and renal interstitial fibrosis. These effects parallel the significant down-regulation of pro-fibrotic gene markers, pro-inflammatory cytokines (TNF-α, IL-6, and MCP-1) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase components, such as gp91^{phox}, p47^{phox}, and p67^{phox}. At the same time, cardio-protective properties of renalase are also evident, as well as hypertension alleviation, cardiac hypertrophy and interstitial fibrosis mitigation, as well as cardiac remodeling prevention via profibrotic genes down-regulation and decreased phosphorylation of ERK-1/2 (41). Moreover, the observation that renalase likely influences the activation and infiltration of macrophages, including their polarization toward the M2 (CD163) phenotype, and suppresses M1-like (CD68) cells, which confirms the proposed hypothesis of renalase functioning as an anti-inflammatory agent. Finally, cardiac fibrosis evaluation, determined by Masson staining, demonstrates that renalase-supplemented animals have been shown to have less matrix deposition and cardiac fibrosis and expression of TIMP-1 and TGF-β, whereas the expression of MMP-1 was upregulated in renalase-treated animals. In the latest research demonstrates that by measuring renalase expression in kidney biopsies in patients with diabetic nephropathy, and in mice with renalase deficiency, renalase exerts a significant protective outcome (38). As evidenced, mesangial hypertrophy, renal inflammation, and pathological injury in animals with diabetes mellitus were more significant in comparison with control mice, whereas in animals with renalase up-regulation, the renal injuries were attenuated. Renalase apparently mitigates high glucose-induced profibrotic gene expression and p21 expression by suppression of ERK½ signaling. Presumably owing to its reno-protective behavior, renalase may be used for amelioration of nephropathy in patients with diabetes mellitus. Similarly, by impediment of the same signaling network, ERK½, including p38, renalase promotes significant mitigation of pressure overload-induced heart failure occurring in rats (40). Such results benefit renalase as a possible left ventricular hypertrophy biomarker, implying its advantage as a potential option for heart failure therapy. Specific single nucleotide polymorphisms evidenced in the renalase gene have been most recently shown to be associated with increased risk for several diseases (56-58). In particular, plasma renalase is documented to be increased in patients presented with unstable angina pectoris and metabolic syndrome (56), whereas the renalase rs10887800 polymorphism implies a significant association with unstable angina and metabolic syndrome development. Furthermore, the perception that the renalase Glu37Asp polymorphism is associated with left ventricle hypertrophy in females with aortic stenosis, and likely alters the binding affinity of the hypoxia- and hypertrophy-related transcription factors, provides proof of the principle that renalase presumably has a role in in hypertrophic response (57). Another clinically relevant setting for renalase determination may be patients with acute coronary microvascular dysfunction (59), providing a role for renalase as a possible biomarker for ischemia. However, renalase demonstrates the ability to predict coronary microvascular dysfunction (CMD) after multivariable adjustments (Framingham risk score), indicating its elevation in response to ischemia from acute CMD, deeming it a possible biomarker for ischemia (59). The observation of renalase's multi-functionality has already been reviewed elsewhere (34, 35, 60), providing the framework for renalase's subsequent experimental research regarding its emerging potential in the modulation of the cardio-renalaxis. If proven that renalase constitutes a missing patho-physiological link in the interplay between the kidneys and the heart, and that it may be used as a relevant cardio-protective agent for patients suffering from chronic kidney disease, it will present an outstanding value for mitigation of cardiovascular disease in patients on dialysis as well as for patients after undergoing kidney transplantation.

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Renalase and gastrointestinal system

The protective effects of renalase in the aforementioned settings of acute kidney and heart injuries has served to nominate this pro-survival factor for a new introduction into the context of another acute injury, the murine model of acute pancreatitis (18). The research however demonstrated that cerulenin-induced acute pancreatitis was significantly mitigated, both *in vitro*, and *in vivo*, when recombinant renalase was administered (prophylactically or therapeutically) after the injury, and that renalase-knocked-out animals exerted a greater severe pancreas injury. This evidence implies that renalase presumably mediates inflammation, at least in part, by hindering the accumulation, activation, and polarization of macrophages (M1 to M2), and macrophage-dependent IL-6 secretion. Levels of renalase in plasma are significantly decreased at the onset of acute pancreas lesion, indicating renalase to be a diagnostic or predictive marker. The noteworthy observation of this research is that plasma renalase markedly increases, far above the basal levels, during the later stage of the injury, indicating renalase biology far beyond being simply a pro-survival factor. Indeed, renalase has been suggested as a factor included in tissue recovery, as well as a pro-fibrotic agent (61). The acknowledgement that renalase affects Ca^{2+} signaling, *via* activation of its receptor PMCA4b, as previously mentioned, and the hypothesis that renalase protects against acute pancreatitis by modulating Ca^{+} transport, provides proof of the principle that renalase administration may be a relevant approach for acute pancreatitis patients. Besides mitigating pancreatic injury, the protective effects of renalse are observed in the following study of oxidative liver damage (62), more precisely in the murine model of ischemia/reperfusion injury that was superimposed on fatty liver disease. Similarly, to the protective effects on pancreatic tissue, recombinant renalase administration preserves the liver phenotype (necrotic area, the level of apoptosis, and the serum con-centration of ALT, AST, and LDH) both *in vivo* and *in vitro*. The underlying mechanism of renalase's cyto-protection is likely the reduction of reactive oxygen species generation, and the amelioration of the mitochondrial function *via* SIRT1 activation. It is worth mentioning that sirutin 1 (SIRT1) represents a histone deacetylase, localized in the nucleus and cytosol, pertaining to the sirtuin family (1-7), a class of nicotinamide adenine dinucleotide (NAD+)-dependent enzymes with multiple metabolic and pro-survival functions (63). Sirtuin 1 is vastly included in the regulation of cell survival in response to different stimuli, is associated with lifespan, and is gradually reduced with the onset of human aging, whereas its deficiency likely promotes age-related diseases (63). In this particular research (62), evidence shows that the lack of renalase leads to the down-regulation of SIRT1 expression and activity, and that recombinant renalase application regulates the expression and activation of SIRT1. In line with these findings, NAD+ represents the essential substrate for sirtuins (including sirtuin 1), whereas it has already been acknowledged that renalase may oxidize α-NADH, thus converting it to β-NAD+. Such results imply that renalase, *via* NAD+ levels elevation, likely upgrades the expression and the activity of sirtuin 1. Nonetheless, these results promote renalase as a relevant approach for liver oxidative injury mitigation. If confirmed that renalase may upgrade the activities of sirtuins, as already evidenced with SIRT1 (62) and SIRT3 (5), this finding would open up an entirely new area of research for renalase scrutiny. Regarding further benefits in liver protection (16), it is reported that renalase is significantly up-regulated in liver tissues that have undergone the ischemia/reperfusion process, and that these increased levels may be effectively suppressed by anti-oxidant therapy (16). Such responsiveness to oxidative stress provides renalase the feasibility of becoming a marker for the assessment of liver ischemic injury, particularly in patients subjected to liver surgery. Finally, the expression of renalase is increased in the mice model measured by fasting-induced oxidative stress, followed by the activation of NF-κβ p65 (19), and is considered to be a mechanism of intestinal anti-oxidative protection. When administered together, the results of these studies, beyond indicating renalase as a pro-survival factor, imply the possibility that the environment, as well, may play a part in modulating the levels of renalase, initially in tissues, and subsequently in the plasma. Such observation further underscores the role of renalase in the setting of the acute injuries, and emphasizes the need for its expanded scrutiny.

Renalase and cancer

Albeit not extensively researched in cancer pathology, most up to date knowledge of renalase's potential roles in pancreatic cancer and malignant melanoma has raised the perception that it may be also used for additional research in oncology. Moreover, it may be hypothesized that renalase's pivotal mechanisms such as acting as a context-dependent interference with ERK1/2, PI3K/Akt, signal transducer and activator of the transcription 3 (STAT3) signaling network including a positive feedback loop with STAT3 (4, 45) may be exploited by cancer cells aiming towards their proliferation and survival. It is initially documented that several types of cancer express increased levels of renalase: these cancers include pancreatic, bladder, breast and melanoma (35). Moreover, the study of pancreatic ductal adenocarcinoma (23), reveals that renalase demonstrates a two-fold increase in diseased pancreatic tissue, in comparison to healthy pancreatic tissue, and, over an average three-year mortality, generally implies that renalase likely promotes tumor cell survival and growth. Additionally, *in vitro* research argues that renalase administration increases pancreatic cancer cells survival rate from twofold to fivefold (23, 35). The same study further confirms that the inhibition of renalase signaling by siRNA or by inhibitory antibodies lessens the viability of pancreatic cancer cells, and enhances the apoptosis and cycle

arrested interruption of tumorous cells (23, 35) Taken together, these findings indicate that renalase-mediated signaling in cancer, if up-regulated, plays a decisive role in the pathophysiology of pancreatic cell carcinoma, making way for the possibility that the inhibition of the renalase signals may represent the anticipation of pancreatic cancer therapy. Moreover, renalase likely exhibits the prognostic potential for pancreatic cancer, or potentially, as a surrogate marker for treatment response or disease recurrence (23, 35). In a more recent study (22), regarding the identical pathohistological type of tumor (pancreatic ductal adenocarcinoma), increased circulating renalase concentration is demonstrated to be increased in both, in both premalignant and malignant tissues, compared to normal pancreatic cells, and is associated with worsened tumor characteristics, including greater angiolymphatic invasion, and greater node positive disease. Accordingly, overall survival is evidenced to be worsened in patients with increased renalase levels. Plasma renalase also predicts whether patients with locally advanced/borderline resection able pancreatic carcinoma should undergo resection. Collectively, elevated levels of renalase in premalignant pancreatic tissue plasma is associated with the nature of advanced tumors, therefore, its plasma concentration correlates with the clinical presentation of the disease, with a decreased level of overall survival and with reduced resect ability for locally advanced/ borderline cancer patients (22). Taken together, renalase shows some degree of promise as a novel tissue and serological biomarker in pancreatic ductal adenocarcinoma, and may presumably guide therapies, including resect ability in cases of pancreatic cancer. Moreover, the expression of renalase suggests its potential role in tumor biology and pathophysiology, upholding the potential for therapies by inhibiting the pro-survival effects of renalase in pancreatic ductal adenocarcinoma.

In line with prior discussions, the renalase expression is further assessed in melanoma, a disease presented with significant dysregulation of the signaling pathways that have been indicated to be under the supervision of renalase (MAPK, PI3K/Akt and JAK/STAT). The study presented out-standing evidence that renalase expression progressively increases from healthy skin tissue, to benign nevi and primary malignant melanoma, and that it is significantly increased in metastatic melanoma (24, 35). Besides indicating increased levels in primary melanomas, its significant expression was detected in CD163+ (M2-like) tumor-associated macrophages. Furthermore, renalase tumor expression (in clinical specimens) inversely correlates with disease-specific survival, implying the particular role of renalase in the pathophysiology of malignant melanoma (24). Renalase inhibition by antibodies, such as derived monoclonal antibody m28, or a renalase-derived inhibitory peptide therapy, decreases melanoma cell survival, and studies show that anti-renalase therapy blocks tumor growth within in vivo experimental models. Within a pathophysiological context, tumor cells exhibit increased apoptosis related to p38 MAPK-mediated Bax activation, followed by increased expression of the cell-cycle inhibitor p21. Moreover, the receptor for renalase, PMCA4b, mediates renalase-dependent STAT3 and ERK1/2 phosphorylation in melanoma cells, whereas dysregulating renalase signaling likely induces the polarization of macrophages towards M2 subclass, which presumably promotes tumor progression. Overall, if dysregulation of renalase signaling promotes the survival of cancer cells, a therapeutic approach objecting to halt these signals, which would therefore inhibit tumor growth, may vastly contribute to the holistic management of melanoma (24). Accordingly, inhibition of renalase expression in immune and host cells is associated with tumor rejection in murine melanoma models, and when rechallenged by another administration of tumor cells fails to result in subsequent tumor development (25), as shown with mice subjected to the wild-type of melanoma, Tumor regression may be benefitted by renalase signal suppression, due to anti-renalase ensuing tumoricidal effects, by effectively tailoring the tumor microenvironment, emitting host-in-dependent, cytotoxic and growth inhibitory effects upon the tumor cells (25). Accordingly, mice lacking the renalase gene exhibit the regression of melanoma in a T-cell-dependent fashion. In line with these findings, the anti-renalase antibodies upgrade the activity of anti-PD-1 in two aggressive murine melanoma models that show poor responsiveness to PD-1 inhibitors, which have been shown to strongly endure the development of anti-renalase antibodies with PD-1 inhibitors, being a potentially effective therapy for melanoma which is resistant to anti-PD-1.

Regarding renalase expression in renal tumors, it is demonstrated that the chromophobe renal cell carcinoma and papillary renal cell carcinoma renalase tissue expression is significantly up-regulated in comparison to control group findings, strongly correlating with the Fuhrman grades of tumors (26). These perceptions nominate renalase as an applicable biomarker for the discrimination of renal cancer grades, whereas anti-renalase therapy seeks the possibility of future anti-cancerous potential. Moreover, beyond the observation that renalase widely exists in various mammary gland cells, its expression is demonstrated to be significantly higher in the estrogen receptor (ER)-positive breast cancer, compared with control tissue, and positively correlates with p-ERK1/2 expression (27). These observations imply the potential for renalase to become a novel biomarker for ER-positive breast cancer, and a potential therapeutic target for ER-positive/HER2-negative subtype cancer. ER expression, including the malignant cell proliferation and growth, may be obtained through the p-ERK1/2 pathway, as already demonstrated, as previously discussed.

Moreover, using immune-localization to resolve the particular types of tumorous cells that relate to renalase up-regulation, it is concluded that melanoma and tumor-associated macrophages significantly correlate with renalase expression (34). Collectively, this collective body of data supports the

hypothesis that molecule silencing and suppressing the effects of renalase for different types of cancer may be entirely effective as anti-cancer therapy, therefore these types of investigations should be highly encouraged and supported.

Conclusion

The results of the aforementioned research establish renalase as a relevant pro-survival agent in several injury settings, providing the potentially profound therapeutic utility of renalase-based therapy for acute tissue and organ injury (myocardial infarction, toxic and ischemic AKI, ischemic liver injury, acute pancreatitis). The data for renalase signaling inhibition, particularly regarding cancers, is also compelling. Conversely, another key goal may be to research the anti-renalase antibodies as a relevant therapeutic approach in treating cancer patients (pancreatic cancer and melanoma).

Even though, up until now, substantial progress on renalase biology has been made, proposed mechanisms regarding its uses, activities and effects calls for more intense scrutiny and a deeper understanding of its pathophysiology. This newly acquired knowledge, combined with the analysis of renalase signaling, will allow us the opportunity to create more effective therapy options, those which are eagerly awaited, and produce ongoing clinical settings for further exploration of renalase and its multi-functionality. Greater understanding of the complete pathophysiology of this somewhat enigmatic, however biologically powerful molecule, may lead to its broad clinical utilization, therefore, vast apprehensions exist regarding its future analysis and promising potential towards clinical research.

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POTENCIJALNA KORIST MERENJA RENALAZE U KLINIČKOJ PRAKSI – REZULTATI PRETKLINIČKIH STUDIJA

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Na osnovu rezulata dobijenih na projektu *Mammalian Gene Collection* 2005. godine otkriven je novi molekul, koji se sintetiše i sekretuje u tkivu bubrega, posledično nazvan *renalaza*. Ekspresija renalaze inicijalno je dokazana u proksimalnim tubulima, ali su dodatna istraživanja pokazala to da se u značajnoj meri može detektovati i u ostalim organima, primarno u tkivu miokarda, zatim u nervima, tkivima pankreasa, jetre i creva, skeletne muskulature i oka. Na osnovu rezulata nedavnih onkoloških studija, značajna ekspresija renalaze u velikom procentu postoji i u malignom tkivu pankreasa, dojke, bubrega i melanoma, uz hipotezu da ovaj flavoprotein potencijalno funkcioniše kao molekulski pokretač za pojedine karcinome. Rezultati novih istraživanja ukazuju na to da postoji visok stepen ekspresije renalaze u humanoj posteljici, od najranijih faza razvoja, sugerišući na njenu relevantnu ulogu tokom gestacije i razvoja ploda. Analiza enzimske aktivnosti renalaze, posebno njene uloge u katabolizmu kateholamina i održanju koncentracije u plazmi, implicira na potencijalnu ulogu u regulaciji krvnog pritiska i očuvanju kardiovaskularnog zdravlja. Pored enzimskog potencijala, renalaza se smatra i molekulom sa citokinskim efektima, naročito u slučajevima akutnih povreda. Na osnovu rezulatata dobijenih pomoću istraživanja na animalnim modelima akutnih oštećenja različitih organa (bubreg, srce, jetra), u kojima je dokazano da administracija renalaze može značajno da umanji stepen lezije tkiva i omogući preživljavanje, ovaj biološki potentan protein smatra se potencijalnom terapijskom opcijom za različite lezije.

Ovaj pregledni rad sumira i daje kritički osvrt na najnovije rezultate dobijene u pretkliničkim studijama, uz potenciranje plejotropije renalaze u zaštiti tkiva i organa (bubreg, srce, jetra, creva) od ishemijskih i toksičnih povreda. Dodatno je obrađena uloga renalaze kao faktora za preživljavanje tumorskih ćelija, s obzirom na to da je dokazano da disregulacija signalizacije renalaze omogućava preživljavanje i rast ćelija melanoma i raka pankreasa.

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Ključne reči: *renalaza, fibroza srca, fibroza bubrega, MAPK, tumorski makrofagi*